2/pts

"Microparticles for pulmonary administration"

The present invention relates to the domain of microparticles intended to be administered via the pulmonary route.

A bibliographical study has made it possible to demonstrate that a great deal of research relating to this technology has been carried out.

Aerosols for releasing therapeutic agents into the respiratory tracts have been described for example (Adjei, A and Garren, J. Pharm. Res., 7: 565-569 (1990); and Zanen, P. and Lamm, J.W.J. Int. J. Pharm., 114: 111-115 (1995)). The respiratory tracts comprise the upper respiratory tracts, which include the larynx and the oropharynx, and the lower respiratory tracts, which include the trachea which extends into bifurcations: the bronchi and the bronchioles. The terminal bronchioles then divide into respiratory bronchioles which lead to the ultimate zone of the respiratory system, the pulmonary alveoli, also named the deep lung (Gonda, I. "Aerosols for delivery of therapeutic and diagnostic agents in the respiratory tract", in Critical Reviews in Therapeutic Drug Carrier Systems, 6: 273-313 (1990)). The deep lung, or the alveoli, is (are) the main target for therapeutic aerosols, by inhalation, intended for the systemic pathway. Aerosols intended to be inhaled have already been used for the treatment of local pulmonary disorders, such as asthma and cystic fibrosis (Anderson et al., Am. Rev. Respir. Dis., 140: 1317-1324 (1989)). In addition, they can be used for the systemic release of peptides and of proteins (Patton and Platz, Advanced Drug Delivery Reviews, 8: 179-196 (1992)). However, a certain number of difficulties are encountered when the intention is to apply the release of medicinal products

by the pulmonary route to the release of macromolecules. Among these difficulties, there is the denaturation of the protein during nebulization, a significant loss of the amount of medicinal products inhaled in the oropharynx (which often exceeds 80%), poor control of the area of deposition, poor reproducibility of the therapeutic results due to the variations in respiratory models, too rapid an absorption of the medicinal products, generating local toxic effects, and phagocytosis by the macrophages of the lung.

The human lung can rapidly eliminate or degrade hydrolyzable products deposited in the form of aerosols, this phenomenon generally occurring over a period of between a few minutes and a few hours. In the upper pulmonary tracts, the ciliated epithelium contributes to the "mucociliary escalator" phenomenon by which particles are led from the pulmonary tracts to the mouth (Pavia, D. "Lung Mucociliary Clearance, "in "Aerosols and the Lung: Clinical and Experimental Aspects, Clarke, S.W. and Pavia, D., Eds., Butterworths, London, 1984.; Anderson et al., Am. Rev. Respir. Dis., 140: 1317-1324 (1989)). In the deep lung, the alveolar macrophages are capable of phagocytosing particles immediately after they have been deposited.

Local and systemic therapies by inhalation generally allow controlled and relatively slow release of the active principle (Gonda, I., "Physico-chemical principles in aerosol delivery", in: Topics in Pharmaceutical Sciences 1991, D.J.A. Crommelin and K.K. Midha, Eds., Stuttgart: Medpharm Scientific Publishers, pp. 95-117 (1992)). The slow release of the therapeutic aerosol may prolong the period of time for which the medicinal product administered remains in the pulmonary tracts or in the acini, and decrease the rate of entry of the medicinal products into the blood stream. Thus,

the patient's tolerance is increased by reducing the frequency of the administrations (Langer, R., Science, 249: 1527-1533 (1990); and Gonda, I. "Aerosols for delivery of therapeutic and diagnostic agents to the respiratory tract", in Critical Reviews in Therapeutic Drug Carrier Systems 6: 273-313 (1990)).

Among the drawbacks represented by dry powder formulations, there is the fact that powders of ultrafine particles have flow and nebulization properties which are generally poor, leading to the production of aerosol fractions which are admitted into the respiratory system relatively slowly, these fractions of the inhaled aerosol generally being deposited in the mouth and in the throat (Gonda, I., in Topics in Pharmaceutical Sciences 1991, D. Crommelin and K. Midha, Editors, Stuttgart: Medpharm Scientific Publishers, 95-117 (1992)).

The main problem encountered with most aerosols is the particulate aggregation generated by the interparticle interactions, such as the hydrophobic, electrostatic and capillary interactions. An effective therapy by inhalation of dry powder for both the immediate and sustained release of therapeutic agents, both locally and systemically, requires the use of a powder having minimal aggregation which makes it possible to avoid or at least to suspend the mechanisms of natural clearance of the lung until the moment when the active principle is released.

There is currently a need for improved inhalation aerosols intended for the pulmonary release of therapeutic agents. Similarly, there is currently a need for medicinal product supports which are capable of releasing the medicinal product in an effective amount in the pulmonary tracts or in the alveolar regions of the lungs.

In addition there is also a need for medicinal product supports which may be used as inhalation aerosols which are biodegradable and which make it possible to release the medicinal products in a controlled manner in the respiratory tracts and the alveolar region of the lungs, and similarly, there is a need for particles for the release of medicinal product in the lungs, which have improved nebulization properties. These investigations tend to show that it is difficult to prepare microparticles which correspond to the criteria imposed on them by them being used under effective conditions.

In order to exhibit sufficient effectiveness, these microparticles must not be damaged during administration, when they pass into nebulized form. The bioavailability of these microparticles must reach a sufficiently high value; however, the bioavailability of the microparticles of the prior art does not generally exceed 50%, due to a low level of deposition of the microparticles in the alveolar pulmonary regions.

In addition, in order to conserve their effectiveness during pulmonary administration, the microparticles, once deposited in the alveoli, must be sufficiently stable in the mucus of the surface of these alveoli.

Thus, it may prove interesting to prepare microparticles for immediate or delayed release, locally or systemically; however, these microparticles generally have an external layer the thickness of which relative to the diameter of said particle is not insignificant.

The microparticles according to the invention consist of a core containing the active material coated with a layer of coating agent deposited by the supercritical fluid technique. This particular structure

distinguishes them from the microparticles of the prior art, which are matricial microspheres obtained using techniques of emulsifying-evaporating solvent, of extracting solvent with aqueous phases or of nebulization-drying organic solvent.

Consequently, the present invention relates to biocompatible microparticles intended to be inhaled, comprising at least one active principle and at least one layer coating this active principle, which is the external layer of said microparticles, said external layer containing at least one coating agent, said microparticles having a mean diameter of between 1 µm and 30 µm and an apparent density of between 0.2 g/cm^3 and 0.8 g/cm^3, and it being possible to obtain them according to a method comprising the essential steps which are bringing together a coating agent and an active principle and introducing a supercritical fluid, with stirring in a closed reactor.

These microparticles do not aggregate when they are administered and may, optionally, allow sustained release of the active principle. The microparticles according to the invention exhibit a bioavailability of greater than 60%, and preferably greater than 80%, due to an improvement in the level of deposition of the particles in the alveolar pulmonary regions.

It has thus been demonstrated that the implementation of a method for preparing microparticles using a "supercritical fluid" technique using, as a coating agent, judiciously chosen biocompatible materials makes it possible to obtain microparticles of controlled size and which have a surface finish such that said microparticles do not aggregate and deposit in the alveolar pulmonary regions.

The biocompatible microparticles intended for

inhalation according to the invention have an external layer comprising a coating agent which prevents these particles aggregating with one another. The degree of covering of the surface area of the particles is at least greater than 50%, preferably greater than 70%, even more preferentially greater than 85%. The quality of this coating is essentially due to the supercritical fluid technique.

Said method comprises two essential steps which are bringing together a coating agent and an active principle and introducing a supercritical fluid in order to ensure the coacervation of the coating agent. It clearly emerges from the remainder of the description that these two steps do not have to be carried out in the order stated.

The first method for preparing the microparticles according to the invention differs from the second method by the fact that the coating agent is at no moment in solution in the fluid in the liquid or supercritical state.

Specifically, a first implementation of the method according to the invention comprises the following steps:

- suspending an active principle in a solution of at least one substantially polar coating agent in an organic solvent,
  said active principle being insoluble in the organic solvent,
  said substantially polar coating agent being insoluble in a fluid in the supercritical state,
  said organic solvent being soluble in a fluid in the supercritical state,
- bringing the suspension into contact with a fluid in the supercritical state, so as to desolvate in a controlled way the substantially polar coating

agent and ensure its coacervation,

- substantially extracting the solvent using a fluid in the supercritical state and discharging the supercritical fluid/solvent mixture,
- recovering the microparticles.

The fluid used for the implementation of this first method is preferably liquid CO_2 or CO_2 in the supercritical state.

The organic solvent used for the implementation of this first method is generally chosen from the group consisting of ketones, alcohols and esters.

The supercritical fluid is brought into contact with the suspension of active principle containing the coating agent in solution by introducing the supercritical fluid into an autoclave which already contains the suspension.

When the supercritical fluid used is CO_2, it is possible to use CO_2 in the liquid form or to directly use CO_2 in the supercritical state.

According to another variant, it is also possible to bring the suspension into contact with liquid CO_2 which will then go into the supercritical state by increasing the pressure and/or the temperature in the autoclave in order to extract the solvent.

When use of the liquid CO_2 variant is chosen, the temperature is preferably chosen between 20 and 30°C and the pressure between 80 and 150 10^5 Pa. When the supercritical CO_2 variant is used, the temperature is generally chosen between 35 and 60°C, preferably between 35 and 50°C, and the pressure between 80 and 250 10^5 Pa, preferably between 100 and 220 10^5 Pa.

The mass of organic solvent introduced into the autoclave represents at least 3%, preferably between 3.5% and 25%, of the mass of the supercritical fluid or liquid used to cause the dissolvation of the coating agent. The microparticles obtained by implementing this first method have an external layer virtually free of solvent; the amount of solvent in the external layer is, in fact, less than 500 ppm.

The coating agents which can be used for the implementation of this first method are more particularly:

- biodegradable (co)polymers of α-hydroxycarboxylic acids, in particular homopolymers and copolymers of lactic acid and glycolic acid, and more particularly PLAs (poly-L-lactide) and PLGAs (poly(lactic-co-glycolic acid)),
- amphiphilic block polymers of the poly(lactic acid)-poly(ethylene oxide) type,
- biocompatible polymers of the poly(ethylene glycol), poly(ethylene oxide) type,
- polyanhydrides, poly(ortho esters), poly-ε-caprolactones and derivatives thereof,
- poly(β-hydroxybutyrate), poly(hydroxyvalerate) and poly(β-hydroxybutyrate-hydroxyvalerate) copolymers,
- poly(malic acid),
- polyphosphazenes,
- block copolymers of the poly(ethylene oxide)-poly(propylene oxide) type,
- poly(amino acids),
- polysaccharides,
- phospholipids such as phosphatidyl glycerols, diphosphatidyl glycerols containing C12 to C18 fatty acid chains (DLPG, DMPG, DPPG, DSPG), phosphatidylcholines, diphosphatidylcholines containing C12 to C18 fatty acid chains (DLPC, DMPC, DPPC, DSPC), diphosphatidylethanolamines

containing C12 to C18 fatty acid chains (DLPE, DMPE, DPPE, DSPE), diphosphatidylserine containing C12 to C18 chains (DLPS, DMPS, DPPS, DSPS), and mixtures which contain the phospholipids mentioned,

- fatty acid esters such as glyceryl stearates, glyceryl laurate, cetyl palmitate, or mixtures which contain these compounds,
- mixtures which contain the abovementioned compounds.

The implementation of the second method according to the invention consists in suspending an active principle in a supercritical fluid containing at least one coating agent dissolved therein, and then in modifying the conditions of pressure and/or of temperature of the environment so as to ensure the coacervation of the particles, by precipitation of the coating agent around the particles of active principle, i.e. to ensure the coacervation of the particles by physicochemical modification of the environment.

The coating agents which can be used for the implementation of this second method are more particularly:

- phospholipids such as phosphatidyl glycerols, diphosphatidyl glycerols containing C12 to C18 fatty acid chains (DLPG, DMPG, DPPG, DSPG), phosphatidylcholines, diphosphatidylcholines containing C12 to C18 fatty acid chains (DLPC, DMPC, DPPC, DSPC), diphosphatidylethanolamines containing C12 to C18 fatty acid chains (DLPE, DMPE, DPPE, DSPE), diphosphatidylserine containing C12 to C18 chains (DLPS, DMPS, DPPS, DSPS), and mixtures which contain the phospholipids mentioned,
- mono-, di-, triglycerides in which the fatty acid chains range from C4 to C22, and mixtures

containing them,
- mixtures of glycerides and of esters of polyethylene glycol,
- cholesterol,
- fatty acid esters such as glyceryl stearates, glyceryl laurate or cetyl palmitate,
- mixtures which contain the abovementioned compounds.

The biodegradable or bioerodible polymers soluble in a supercritical fluid may also be used in this second method.

The coacervation (or aggregation) of a coating agent is caused by physicochemical modification of an environment containing an active substance in suspension in a solution of a coating agent in a solvent, said solvent being a supercritical fluid.

The supercritical fluid preferentially used is supercritical CO_2 ($SCCO_2$), the typical initial functioning conditions of this second method will be approximately 31 to 80°C and the pressures will be 75 to 250 10^5 Pa, although higher values may be used for one or other of the two parameters, or both, on condition, of course, that the higher values have no harmful or degradation effect on the active principle being covered, or on the coating agents.

Moreover, it is also possible to choose other fluids commonly used as supercritical fluids. Mention will be made in particular of ethane, which becomes supercritical above 32°C and 48 10^5 Pa, nitrogen dioxide, the critical point of which is 36°C and 72 10^5 Pa, propane, the critical point of which is 96°C and 42 10^5 Pa, trifluoromethane, the critical point of which is 26°C and 47 10^5 Pa, and chlorotrifluoromethane, the critical point of which is 29°C and 39 10^5 Pa.

This second method involves suspending, in a closed stirred autoclave, an active principle which is insoluble in the supercritical fluid, said supercritical fluid containing a coating agent which is in the state of a solute.

The pressure and/or the temperature are then modified so as to decrease the solubility of the coating agent in the fluid. Thus, the affinity of the coating agent for the active principle increases such that this coating adsorbs around the active principle. Once this coating agent is deposited over the active principle, the autoclave is depressurized and the microparticles are recovered.

To implement this second method, the active principle to be covered and the coating agent(s) are placed in an autoclave equipped with a stirrer, and then the system is pressurized by introducing into the autoclave a fluid presented under supercritical conditions. The temperature and/or the pressure inside the autoclave is then modified in a controlled and regulated way so as to gradually decrease the solubility of the coating agent(s). When the solubility of this or these coating agent(s) in the supercritical fluid decreases, it (they) precipitate(s) and the affinity of these agents for the surface of the active principle leads to them being adsorbed onto this surface. A variant of this method consists in placing the coating agent in the autoclave before introducing the active principle therein or while simultaneously introducing therein the active principle and a fluid capable of passing into the supercritical state. The pressurization of the autoclave to produce a supercritical fluid state will then cause the coating agent to dissolve in said supercritical fluid.

According to another variant of the method, the active principle is placed in an autoclave equipped with a stirrer, and the coating agent is placed in a second autoclave equipped with a stirrer, into which the fluid capable of passing into the supercritical state is introduced. The coating agent is brought to the state of a solute by increasing the temperature and the pressure, and is then transferred into the autoclave which contains the active principle.

The coating agent is thus deposited such that this agent covers the surface of the active principle.

The active principle may be in the form of a liquid, which may thus form an emulsion in the supercritical fluid, of preformed solid particles, and in particular of microparticles optionally already coated, for example, with mono- or disaccharides. The stirring speeds may range between 150 and 700 rpm for the solid particles and between 600 and 1 000 rpm when the active principle is a liquid.

Such stirring ensures that the active principle is suspended in the supercritical fluid when the latter is introduced. The supercritical conditions are produced by modifying the temperature and/or the pressure inside the autoclave. Thus, when the supercritical fluid is CO_2, the temperature of the autoclave is between 35 and 80°C, preferably between 35 and 50°C, and the pressure is between 100 and 250 10^5 Pa, and preferably between 180 and 220 10^5 Pa.

When the supercritical fluid is ethane, the temperature of the autoclave is between 35 and 80°C, preferably between 35 and 50°C, and the pressure is between 50 and 200 10^5 Pa, and preferably between 50 and 150 10^5 Pa.

When the fluid is propane, the temperature of the

autoclave is between 45 and 80°C, preferably between 55 and 65°C, and the pressure is between 40 and 150 10^5 Pa.

The coating agent is introduced into the autoclave at the same time as the supercritical fluid or before the supercritical fluid is introduced into the autoclave. In any event, in order to ensure good solubilization of the coating agent in the supercritical fluid, the system is maintained at equilibrium with stirring, the suitable concentration of active principle and of coating agent is established as a function of the desired microparticles and this equilibrium is left for one hour with stirring. The temperature and the pressure are then modulated at a rate sufficiently slow to completely transfer the coating agent(s) from the supercritical fluid to the surface of the active principle, and the system is depressurized in order to isolate the microparticles, which are removed from the autoclave.

The microparticles according to the present invention have a diameter of between 1 μm and 30 μm, preferably of between 1 μm and 15 μm, and even more preferably of between 2 μm and 10 μm, and an apparent density of between 0.02 g/cm^3 and 0.8 g/cm^3, and preferably of between 0.05 g/cm^3 and 0.4 g/cm^3.

The active principle/coating agent mass ratio of these microparticles is preferably between 95/5 and 5/95.

In the case of controlled-release microparticles, the amount of active principle is small compared to the coating agent, and the active principle/coating agent mass ratio is then between 5/95 and 20/80; on the other hand, when the coating is intended to stabilize the particle, in particular when the microparticle is an immediate-release microparticle, the active principle/-

coating agent mass ratio is generally between 95/5 and 70/30, and preferably between 95/5 and 80/20.

The coating agents of the microparticles according to the invention advantageously belong to the following families:

- biodegradable (co)polymers of α-hydroxycarboxylic acids, in particular homopolymers and copolymers of lactic acid and glycolic acid, and more particularly PLAs (poly-L-lactide) and PLGAs (poly(lactic-co-glycolic acid)),
- mono-, di-, triglycerides in which the fatty acid chains range from C4 to C22, and mixtures containing them,
- mixtures of glycerides and of esters of polyethylene glycol,
- cholesterol,
- amphiphilic block polymers of the poly(lactic acid)-poly(ethylene oxide) type,
- biocompatible polymers of the poly(ethylene glycol), poly(ethylene oxide) type,
- polyanhydrides, poly(ortho esters), poly-ε-caprolactones and derivatives thereof,
- poly(β-hydroxybutyrate), poly(hydroxyvalerate) and poly(β-hydroxybutyrate-hydroxyvalerate) copolymers,
- poly(malic acid),
- polyphosphazenes,
- block copolymers of the poly(ethylene oxide)-poly(propylene oxide) type,
- poly(amino acids),
- polysaccharides,
- phospholipids such as phosphatidyl glycerols, diphosphatidyl glycerols containing C12 to C18 fatty acid chains (DLPG, DMPG, DPPG, DSPG), phosphatidylcholines, diphosphatidylcholines containing C12 to C18 fatty acid chains (DLPC, DMPC, DPPC, DSPC), disphosphatidylethanolamines

containing C12 to C18 fatty acid chains (DLPE, DMPE, DPPE, DSPE), diphosphatidylserines containing C12 to C18 chains (DLPS, DMPS, DPPS, DSPS), and mixtures which contain the phospholipids mentioned,

- fatty acid esters such as glyceryl stearates, glyceryl laurate or cetyl palmitate,
- mixtures of at least two compounds chosen from the abovementioned fatty derivatives and such that they have suitable solubility.

Depending on the coating agent, the solubility in the supercritical fluids and the coating conditions, the first or the second method described above may thus be implemented.

Said active principle may be in the form of a liquid, of a solid powder or of an inert porous solid particle comprising, on its surface, an active principle.

The active principles used are chosen from very varied therapeutic and prophylactic compounds. They are more particularly chosen from proteins and peptides, such as insulin, calcitonin, or analogues of the hormone LH-RH, polysaccharides such as heparin, anti-asthmatic agents, such as budesonide, beclometasone dipropionate and its active metabolite beclometasone 17-monopropionate, beta-estradiol hormones, testosterone, bronchodilators such as albuterol, cytotoxic agents, corticoids, antigens and DNA fragments.

Figure 1 is an electron micrograph of a microparticle obtained according to example 2.

Figure 2 is an electron micrograph of microparticles obtained according to example 3.

The examples which follow illustrate the invention

without limiting the scope thereof.

Example 1

This example illustrates the first method of implementation of the invention.

80 mg of PLGA are solubilized in 80 ml of ethyl acetate. 400 mg of micronized insulin are suspended in the solution thus obtained at 250 rpm and the suspension is placed in an autoclave with a capacity of 1.0 l. Initially, the pressure is increased to 100 10^5 Pa by introducing the liquid CO_2, while at the same time remaining at a constant temperature of 28°C.

The CO_2 in the liquid state mixes with the suspension, thus making it possible to wet the insulin and also making it possible to produce the gradual precipitation of the coating agent.

The CO_2 is taken to the supercritical state by gradually increasing the pressure to 150 10^5 Pa. The temperature is jointly maintained at 40°C. Thus, the ethyl acetate is extracted. These conditions are maintained for 15 minutes and then the CO_2/ethyl acetate mixture is discharged, by decompressing to 75 10^5 Pa, in a separator, while maintaining the temperature at a value greater than 35°C. The ethyl acetate is recovered in this separator and the CO_2 returns to a reservoir.

The ethyl acetate is recovered and the successive cycles of introducing the liquid CO_2, taking it to the supercritical state and discharging the CO_2 + ethyl acetate are repeated until the ethyl acetate is completely eliminated.

The decompression necessarily takes place via the

gaseous phase so as not to reconcentrate any coating agent in the remaining ethyl acetate. After the decompression phase, the operation may be repeated several times by reintroducing CO_2 in order to return to a pressure of 150 10^5 Pa and a temperature of 40°C. Finally, after depressurization and extraction of the CO_2 + solvent mixture, fresh CO_2 is reintroduced, and is taken to the supercritical state in order to completely extract the solvent. The temperature in this case is generally between 35 and 45°C and the pressure between 180 and 220 10^5 Pa.

250 mg of nonaggregated microparticles are thus obtained, which have a mean size of 3 µm, comprising 80 to 90% by weight of insulin and have improved nebulization properties.

Example 2

This example illustrates the second method of implementation of the invention.

150 mg of bovine serum albumin (BSA) prepared by spray-drying and 600 mg of Gelucire® 50/02 in the form of chips are placed in a pressurizable and stirred 0.3 l autoclave equipped with a porous insert.

CO_2 is introduced into the autoclave until a pressure of 95 10^5 Pa is obtained for a temperature of 25°C. The CO_2 is then in the liquid state.

The stirring is begun and set at 460 rpm. The autoclave is then heated to 50°C. The pressure is then 220 10^5 Pa; the CO_2 is in the supercritical state and has a density of 0.805 g/cm^3.

The system is left to equilibrate for one hour. The temperature of the autoclave is then decreased to 19°C

over a period of 38 minutes starting from 50°C. The phase in suspension in the supercritical CO_2 thus transforms into a mixture of liquid and gaseous CO_2, the particles of active principle being in suspension in the liquid CO_2. By then depressurizing to atmospheric pressure microparticles of BSA covered with Gelucire® 50/02 are obtained.

250 mg of nonaggregated particles of BSA, with a mean diameter equal to 10 μm, coated with a layer of Gelucire® 50/02, are thus obtained, the active principle/coating agent mass ratio of which is approximately 30/70. These microparticles have improved nebulization properties.

Example 3

This example illustrates the second method of implementation of the invention.

300 mg of ovalbumin (OVA) prepared by spray-drying and 300 mg of Gelucire® 50/13 in the form of chips are placed in a pressurizable and stirred 1 l autoclave.

CO_2 is introduced into the autoclave until a pressure of 109 10^5 Pa is obtained for a temperature of 23°C. The CO_2 is then in the liquid state.

The stirring is begun and set at 340 rpm. The autoclave is then heated to 35°C. The pressure is then 180 10^5 Pa and the CO_2 is in the supercritical state.

The system is left to equilibrate for one hour. The temperature of the autoclave is then decreased to 16°C over a period of 43 minutes starting from 35°C. The phase in suspension in the supercritical CO_2 thus transforms into a mixture of liquid and gaseous CO_2. By then depressurizing to atmospheric pressure

microparticles of OVA covered with Gelucire® 50/13 are obtained.

300 mg of nonaggregated particles of OVA, with a mean diameter equal to 9 µm, coated with a layer of Gelucire® 50/13, are thus obtained, which have improved nebulization properties.

Example 4

This example illustrates the second method of implementation of the invention.

300 mg of beclomethasone dipropionate in the form of free powder prepared by spray-drying and 50 mg of dilauroyl phosphatidyl glcyerol (DLPG) are placed in a pressurizable 0.3 l autoclave equipped with a porous insert.

CO_2 is introduced into the autoclave until a pressure of 98 10^5 Pa is obtained for a temperature of 23°C. The CO_2 is then in the liquid state.

The stirring is begun, at 460 rpm. The autoclave is then heated to 60°C. The pressure is then 300 10^5 Pa, and the CO_2 is in the supercritical state and has a density of 0.830 g/cm^3.

The system is left to equilibrate for one hour. The temperature of the autoclave is then decreased to 20°C over 65 minutes. The phase in suspension in the supercritical CO_2 thus transforms into a mixture of liquid and gaseous CO_2, the particles of active principle being in suspension in the liquid CO_2. By then depressurizing to atmospheric pressure, microparticles of beclomethazone dipropionate covered with DLPG are obtained.

200 mg of nonaggregated particles of beclomethasone dipropionate, with a diameter equal to 5 μm, coated with a layer of DLPG, are thus obtained, the active principle/coating agent mass ratio of which is approximately 90/10. These microparticles have improved nebulization properties.